Optimization and control of freeze-drying of pharmaceutical proteins: the European project Lyo-Pro

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Optimization and Control of Freeze-Drying of Pharmaceutical Proteins: the European project Lyo-Pro.

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Pharmaceutical proteins have impacted several therapeutic areas, namely cardiovascular, immunological, cancer, hematology, and endocrine. However, the clinical application of these products (normally in aqueous solution) is limited by several problems such as the rapid denaturation during handling, processing and storage with the consequent loss of the biological activity. The protein shelf life is often improved by drying processes to prevent degradation. Since proteins are heat sensitive, drying must be performed at low temperature.

The availability of better technology and equipment will improve the production of therapeutic proteins in lyophilized form, reducing the possibility of introduction of immunogenicity or other undesirable changes in the properties of the product.

The objective of *Lyo-Pro* is to optimize the freeze-drying of pharmaceutical proteins on a scientific basis in order to set up efficient and rational freeze-drying diagrams for industrial manufacturing of commercially used drugs and diagnostic proteins.

Actually the research is mainly focused on:

- improving the control of the nucleation of ice crystals; this will completely modify the freezing step of lyophilization, allowing to better control the structure of the product;
- development of new control tools and controlling devices, to improve the process control (soft and hard sensors);
- tests on lab and pilot scale apparatus, to develop scale up procedures and verify the effect of the innovation in conditions similar to the real ones.

Improving freeze-drying of pharmaceutical proteins needs a multidisciplinary approach; the problem cannot be solved easily with the current knowledge, but a team of experts in different areas (chemists, molecular biologists, engineers, etc) is necessary to understand the mechanism of the fundamental phenomena occurring.

Five industrial partners from four different countries participate: three pharmaceutical companies (**Alfa Wassermann** (I), **bioMerieux** (F) and **Ethypharm** (F)), a freeze-drier manufacturer (**Telstar** (E)) and a SME company (**Asymptote** (UK)). The necessary scientific support will be given by the Lab. of food technology of **INRA** (F) and three Universities (from three countries): a joint group from the Dept. of Chemical Engineering and Electronic Engineering of **Politecnico di Torino** (*Project Co-ordinator*) (I), the Central Laboratory Animal Institute and the Department of Pharmaceutics from **Utrecht University** (NL), the Laboratory of Automation and Process Engineering from **Lyon 1 University** (F).

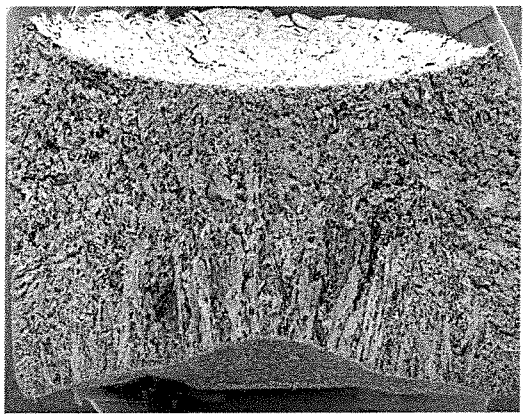

Figure 1 - Spontaneous nucleation

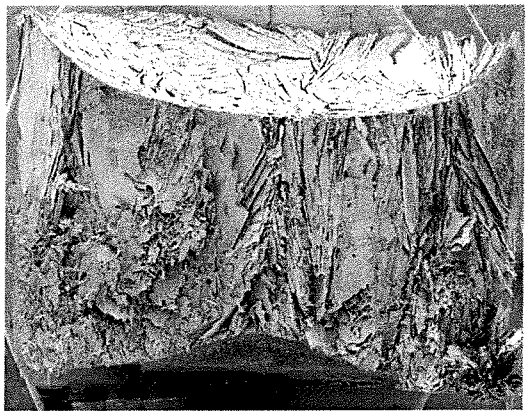

Figure 2 - Forced nucleation

Main projects outputs: scientific based methods to design, to scale-up, and to control industrial freeze-dryers for producing commercial drugs with required quality; avoidance of antigenicity; reduction of waste in production of serological screening tests. New technology in freeze-drying. Guidelines for standardisation of freeze drying procedure.